the art to which the invention pertains. These rejections are most respectfully traversed.

Applicants again wish to direct the Examiner's attention to the basic requirements of a prima facie case of obviousness as set forth in the MPEP § 2143. This section states that to establish a prima facie case of obviousness, three basic criteria first must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine the reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art references when combined must teach or suggest all the claim limitations. The claimed subject matter has not been prima facie obvious by the combination of references relied upon in the rejections and the rejections are traversed.

All of the claims in the present application are either based directly or indirectly on claim 1 which claims:

A metered dose inhaler which comprises a canister fitted with a metering valve which contains a pharmaceutical solution aerosol formulation which comprises:

(i) fluticasone propionate and

(ii) a hydrofluoroalkane (HFA) propellant,

characterised in that the fluticasone propionate is completely dissolved in the formulation;

wherein the canister is fitted into a channelling device which comprises a mouthpiece actuator having an actuator exit orifice of diameter 0.25mm or less.

The claim limitations include a metered dose inhaler comprising a canister fitted into a channelling device which comprises a mouthpiece actuator having an actuator exit orifice of diameter 0.25mm or less. Where are these limitations taught in the prior art applied in the rejections? Neither Weers et al, Davis et al nor Otterbeck et al contains any teaching whatsoever directed to the selection of the dimensions of an actuator orifice which is part of the claimed subject matter and is a preferred aspect of the invention. As noted at page 11, Applicants have found that it is advantageous to use

a smallbiameter, e.g., 0.25 mm or less since this tends to result in a higher FPM and lower throat deposition. See also, page 18, line 22 of the specification and the limitation of claim 33. There is no discussion of these claim limitations in the rejections. In this regard, obvious to try is not the standard of obviousness under more35 USC 103(a).

More particularly, Applicants wish to stress that one skilled in the art, starting with the knowledge of Davis et al would not combine its teaching with that of the teachings of Weers *et al*, since Weers *et al* is from a different technical field to Davis *et al* (and the present application), medicinal suspension formulations and medicinal solution formulations respectively. The technical issues which must be addressed are different for each kind of formulation, for example, Weers *et al* discusses some of the problems that must be overcome in formulating a suspension formulation in column 1, lines 33 to 37 it states that "*If particle size of the suspended material cannot be regulated and aggregation takes place, the valve orifice of the aerosol may clog rendering the dispensing device inoperative or, if a metering valve is employed, it may be rendered inaccurate*." The text then goes on to say that aggregation may lead to "*fast creaming or sedimentation of the suspension*" (column 1, lines 41 to 42). Technical issues of this kind do not need to be addressed when formulating a solution formulation, issues such as droplet size and keeping the medicament in solution are important, issues to which Weers *et al* does not relate as would be appreciated by one of ordinary skill in the art to which the invention pertains.

As a consequence of fact that Weers *et al* describes only suspension formulations (and not solution formulations) of over 65 medicaments and bioactive agents (column 19, line 55 to column 20, line 20) of which fluticasone propionate is one, it follows that selection of an actuator orifice diameter of the small size (less than 0.25mm diameter) claimed cannot be obvious in light of this document since such a small diameter used in conjunction with a suspension aerosol formulation of fluticasone propionate would lead to actuator blockage with the particles of fluticasone propionate. As stated in column 13, lines 35 to 37 of Weers et al "*the mean geometric particle size of the perforated microstructures is preferably about 0.5 - 50 μm*" so a single preferred

particle could be up to 0.05mm (50 μm) in size, which could clearly lead to blockage of an actuator orifice less than 0.25 mm in diameter.

A person skilled in the art wishing to develop an MDI for a solution formulation of fluticasone propionate, on reading Weers *et al* would find this document to be of very little assistance not only due to the fact that it is in a different technical field but also due to its very generic and unspecific nature. The skilled artisan would certainly not select the small orifice diameter as claimed in the present invention in the expectation of any useful results since there is absolutely no motivation in this document for him to do so.

In any event applicants have found that with solution formulations of fluticasone propionate, use of an actuator exit orifice diameter of diameter 0.25mm or less, as claimed in claim 1 of the present application, results in a higher fine particle mass (FPM) and lower throat deposition. This is explained in page 11, line 11 to 12, of the specification and illustrated by the convincing results shown in figures 5 and 6. Such beneficial results could not possibly have been predicted from the disclosure of Weers *et al* and/or Davis *et al*, which are, in fact, totally silent on actuator diameter.

The non-obvious nature of the invention is apparent from the surprising advantages of the claimed MDIs. In this regard, Applicants again most respectfully direct the Examiner's attention to MPEP § 2144.08 (page 2100-114) wherein it is stated that Office personnel should consider all rebuttal argument and evidence presented by applicant and the citation of In re Soni for error in not considering evidence presented in the specification. Accordingly, it is most respectfully requested that this rejection be withdrawn.

It is urged in the Official Action that one cannot attack references individually. However, the references are to be interpreted in light of the level of skill of one of ordinary skill in the art to which the invention pertains. The differences in the teaching of the reference would not be ignored by one of ordinary skill in the art. The claims in the present application specify metered dose inhalers. A Metered Dose Inhaler (MDI) would be understood by one of ordinary skill in the art to utilize a liquefied propellant to expel droplets containing the pharmaceutical product to the respiratory tract as an

aerosol. As noted at page 2, line 15 of Applicants' specification, the efficiency of an MDI is a function of the dose deposited at the appropriate site in the lungs. A nebulizer is completely different as discussed in the last response. The basis of the rejection as stated in the second full paragraph on page 3 of the rejection is that "one skilled in the art would have been motivated to practice the teaching of Davis using other active agents, since Davis is clearly disclosing advantages of the solution for aerosol delivery." However, Davis delivery is with a nebulizer and the present claim limitations specify an MDI. As would be fully appreciated by one of ordinary skill in the art, this motivation does not lead to the claimed invention and should be withdrawn.

The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in applicant's disclosure. In re Vaeck, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). There is no reasonable expectation of success to obtain the presently claimed Metered Dose Inhaler by adding a specific component from Weers to Davis' nebulizer. Accordingly, it is most respectfully requested that this rejection be withdrawn.

Section 2143.03 states that all claim limitations must be taught or suggested by the prior art. In re Royka, 490 F.2d 981, 180 USPQ 580 (CCPA 1974). "All words in a claim must be considered in judging the patentability of that claim against the prior art." In re Wilson, 424 F.2d 1382, 1385, 165 USPQ 494, 496 (CCPA 1970). If an independent claim is nonobvious under 35 U.S.C. 103, then any claim depending therefrom is nonobvious. In re Fine, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988).

As has been previously noted by Applicants, Davis et al. differs in several ways from claim 1 and claims dependent thereon of the present application. As would be appreciated by one of ordinary skill in the art, Davis et al. relates to aqueous systems in a nebulizer and relates to the delivery of aqueous droplets containing drug from the nebulizer. The presently claimed invention relates to non-aqueous hydrofluoroalkane (HFA) propellant systems in a metered dose inhaler and relates to the delivery of fine

particles of medicament. The properties of water and HFA propellants are very different, and a person of ordinary skill in the art would not expect observations of properties in an aqueous system to be applicable to a non-aqueous HFA system. These differences alone would not provide the necessary motivation to modify the Davis et al reference to arrive at the presently claimed invention as it would be understood by one of ordinary skill in the art to which the invention pertains.

Further, a nebulizer operates in a different way from a metered dose inhaler (MDI). A nebulizer is a mechanical device which provides a source of energy, for example, in the form of ultrasonic vibration or air pressure to create **aqueous** droplets of a suitable size for inhalation. In contrast, an MDI comprises an enclosed canister in which liquefied propellant is held under pressure which, in the case of Propellant HFA 134a, is 5 to 6 bar. The nebulizer operates by providing a mechanical means of converting progressively an aqueous-based solution or suspension of medicament into aqueous droplets, while an MDI operates by delivering a metered volume of liquefied propellant containing medicament from within the canister via an atomising orifice. The rapid expansion of the propellant through the atomising orifice provides the energy to produce an aerosol of drug particles of a suitable size for inhalation. The properties of the formulations within these systems are therefore required to be quite different as would be appreciated by one of ordinary skill in the art.

For example, a solution or suspension for nebulization will be aqueous-based, the surface tension and viscosity of which are appropriate to facilitate the formulation of aqueous droplets. In the case of an MDI, the drug is either dissolved or suspended in liquefied propellant, the polarity and vapour pressure of which is important in the effective aerosolisation of the formulation on release via the metering valve. Again, a person of ordinary skill would not apply teachings relating to a nebulizer to an MDI and the necessary motivation to modify the teachings of the prior art are not present and a prima facie case of obviousness has not be established by the combination of references. Applicants' specification may not be used to provide this teaching. In re Fritch, 23 USPQ 1780, 1784(Fed Cir. 1992) ("It is impermissible to engage in hindsight

reconstruction of the claimed invention, using the applicant's structure as a template and selecting elements from references to fill the gaps.).

The drug referred to in Davis et al. is flunisolide; fluticasone propionate is not disclosed.

The technology discussed in Weers et al. relates to suspension formulations comprising a suspension medium having dispersed therein a plurality of perforated microstructures and the suspension medium permeates the perforated microstructures. The claims of the present application relate to a solution formulation, and are not directed to perforated microstructures. Teachings of the Weers et al. document would not be applied to a solution formulation such as that of the present application as would be appreciated by one of ordinary skill in the art to which the invention pertains and the necessary motivation is not present for the reasons noted above.

Weers et al. states that exemplary medicines for use in relation to that invention may be selected from a wide range of compounds of various types. Included within that list of compounds are anti-inflammatories, of which eleven are named. From that length of list of compounds it cannot be reasonably argued that it would have been obvious to the person skilled in the art to substitute flunisolide for fluticasone propionate.

Further, the person skilled in the art would know that one cannot simply substitute one anti-inflammatory compound for another. It is well known by those skilled in the art that different anti-inflammatory compounds have different physical and chemical properties, for example, they will have different densities, solubilities in propellant, solubilities in cosolvents, solubilities in water, and different chemical stabilities in solution. It would not have been obvious to a person of ordinary skill in the art to substitute flunisolide for fluticasone propionate and this aspect of the rejection should be withdrawn.

In claim 2, the low volatility component is present in the formulation at a concentration of 0.5 to 3% w/w.

In the propylene glycol-ethanol-water systems described in Davis et al., propylene glycol and ethanol are primarily used as cosolvents to promote the

solubilisation of the medicament. The droplets leaving the nebulizer and subsequently inhaled by the patient comprise a mixture of water, propylene glycol and ethanol in which a drug is dissolved. In Davis et al.,, it is stated that "the mass median diameter (of droplets) increases...as the percentage of propylene glycol is decreased" (page 89).

In the MDI of the present invention a solubilising agent, in one embodiment ethanol, is primarily used as a cosolvent to solubilise the medicament which, together with the HFA propellant, rapidly evaporates from the aerosol droplets initially expelled from the MDI, so that the particles inhaled largely comprise low volatility component and drug (the drug is likely to be dissolved in the low volatility component, in one embodiment propylene glycol). The low volatility component serves to maintain the desired size of particle which comprises the low volatility component and drug so that the fine particle mass, as defined by the content of stages 3-5 of an Andersen Cascade Impactor, matches better the distribution of the drug particles delivered by the then existing commercialised suspension formulations which contained CFCs (see page 5, lines 3-11). Davis et al. does not address the problem of a particle size distribution which have a higher content of finer particles so that the distribution does not match that of commercialised CFC formulations which can lead to a higher systemic exposure to the aerosol particles due to deep lung penetration which can enhance the undesired systemic effects of drugs.

The fact that the function of the propylene glycol in Davis et al. and the low volatility component in the present application are quite different is further evidenced since the amount of propylene glycol in the formulations in Davis et al. is in the range 25 to 50% v/v (see Table 2 on page 92). In claim 2 of the present application, the concentration of the low volatility component is in the range 0.5 to 3% w/w and there is no motivation to arrive at this concentration which is a claim limitation which cannot be ignored.

The Examiner is of the opinion that the range included in claim 2 directed to the amount of propylene glycol, 0.5 to 3 % w/w, is obvious as Davis *et al* discloses formulations that comprise 5 to 70% propylene glycol (see table 1, page 87). Applicants

most respectfully disagree with the Examiner's assumption, Applicants have not merely optimized the amount of propylene glycol, but have surprisingly found that smaller amounts of propylene glycol, not disclosed in Davis *et al*, have a beneficial effect on fine particle mass to address the problem of particle size distribution in solution formulations.

From the preceding arguments it can be concluded that claims 1-27, 29-31 and 33-38, as amended, are patentable over Davis et al., in view of Weers et al. and the rejection should be withdrawn.

The rejection of claims 1-6, 8-27, 29-31 and 33-38 under 35 U.S.C. §103(a) as being unpatentable over Otterbeck et al. in view of Weers et al. has been carefully considered but is most respectfully traversed in view of the discussion above and the following comments.

As stated above, Otterbeck et al does not contain any teaching whatsoever directed to selection of the dimensions of an actuator orifice and as mentioned above, neither does Weers *et al.*

Otterbeck *et al* is directed to rectal enemas and foams, one skilled in the art would not look at this technical field for teachings in the field of metered dose inhalers for inhalation. The difficulties associated with formulating a solution formulation for inhalation are very different from those which must be overcome when formulating an enema or foam for rectal application. For example, droplet size is of no consequence when formulating a rectal enema or foam, as the medicament does not have to reach deep into the lungs in order to be effective.

The presently claimed invention is specific to Metered Dose Inhalers and this is a claim limitation which cannot be ignored. In this regard, please seen DiversitechCorp. v. Centruyary Stpes Inc. CAFC June 27, 1988 7 USPQ2d 1317

[1] The district court correctly considered all elements of the claims including the preamble. In re Stencel, 828 F.2d 751, 754-55, 4 USPQ2d 1071, 1073 (Fed. Cir. 1987) states:

> Whether a preamble of intended purpose constitutes a limitation to the claims is, as has long been established, a matter to be determined on the facts of each case in view of the claimed invention as a whole.
>
> This purpose, set forth in the [preambles of the] claims themselves, "is more than a mere statement of purpose; and that language is essential to particularly point out the invention defined by the claims." In re Bulloch, 604 F.2d 1362,1365, 203 USPQ 171, 174 (CCPA 1979).

See also Perkin-Elmer Corp. v. Computervision Corp.. 732 F.2d 888, 896, 221 USPQ 669, 675 (Fed. Cir.), cert. denied, 469 U.S. 857 [225 USPQ 7921 (1984) (the limitations appearing in the preamble are necessary to give meaning to the claim and properly define the invention). The MDI of the claimed invention are not obvious from the prior art.

Otterbeck et al. differs in several ways from the amended claims of the presently claimed invention. Otterbeck et al. discloses budesonide solutions for use as the active ingredient in rectal enemas or rectal foams. The present invention relates to HFA propellant systems in a metered dose inhaler (a claim limitation which cannot be ignored) to deliver fine particles of medicament to the lungs.

HFA propellant systems are not disclosed in Otterbeck et al. In Otterbeck et al. it is stated that "the propellant gases preferably used are ... hydrocarbons such as isobutene, –butane or propane/n-butane mixtures". (column 4, lines 19-21.)

None of the Examples in Otterbeck et al. teach the combination of a low volatility component, fro example propylene glycol and ethanol, the Examples teach the addition of propylene glycol or ethanol. In Otterbeck et al. it is stated that "The alcohols used for the purposes of the present invention are preferably propylene glycol, ethanol or isopropanol." (Column 3, lines 36-37.)

In the present invention, as stated above, the low volatility component is added to maintain the desired particle size, however in Otterbeck et al. particle size is not important as the solution is for a different use and a low volatility component is not added for the purpose of maintaining particle size.

Propylene glycol is added merely as a solubilising agent in Otterbeck et al. and the differing function is further evidenced since propylene glycol is added in such large amounts, in Otterbeck et al. 35g in Examples 7, 8 and 9 when budesonide is present at only 0.0182g. The concentration of the low volatility component in claim 2 of the present invention is typically in the range of 0.5-3% w/w and is not suggested by the prior art and this aspect of the rejection should be withdrawn.

The drug referred to in Otterbeck et al. is budesonide; fluticasone propionate is not disclosed in Otterbeck et al.

As previously stated, the person skilled in the art would know that one cannot simply substitute one anti-inflammatory compound for another, it would not have been obvious to one skilled in the art to substitute budesonide with fluticasone propionate. It is well known by those skilled in the art that different anti-inflammatory compounds have different physical and chemical properties, for example, they will have different densities, solubilities in propellant, solubilities in cosolvents, solubilities in water, and different chemical stabilities in solution. Accordingly, it is most respectfully requested that this rejection be withdrawn.

In view of the above comments and further amendments to the claims, favorable reconsideration and allowance of all of the claims now present in the application are most respectfully requested.

Respectfully submitted,
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